Title
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Journal
Integrative and comparative biology, 49(2)

ISSN
1540-7063

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Publication Date
2009-08-01

DOI
10.1093/icb/icp017

Peer reviewed

Cell–cell signaling drives the evolution of complex traits: introduction—lung evo-devo

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Synopsis Physiology integrates biology with the environment through cell–cell interactions at multiple levels. The evolution of the respiratory system has been ''deconvoluted'' (Torday and Rehan in Am J Respir Cell Mol Biol 31:8–12, 2004) through Gene Regulatory Networks (GRNs) applied to cell–cell communication for all aspects of lung biology development, homeostasis, regeneration, and aging. Using this approach, we have predicted the phenotypic consequences of failed signaling for lung development, homeostasis, and regeneration based on evolutionary principles. This cell–cell communication model predicts other aspects of vertebrate physiology as adaptational responses. For example, the oxygen-induced differentiation of alveolar myocytes into alveolar adipocytes was critical for the evolution of the lung in land dwelling animals adapting to fluctuating Phanarezoic oxygen levels over the past 500 million years. Adipocytes prevent lung injury due to oxygen radicals and facilitate the rise of endothermy. In addition, they produce the class I cytokine leptin, which augments pulmonary surfactant activity and alveolar surface area, increasing selection pressure for both respiratory oxygenation and metabolic demand initially constrained by high-systemic vascular pressure, but subsequently compensated by the evolution of the adrenomedullary beta-adrenergic receptor mechanism. Conserted positive selection for the lung and adrenals created further selection pressure for the heart, which becomes progressively more complex phylogenetically in tandem with the lung. Developmentally, increasing heart complexity and size impinges precociously on the gut mesoderm to induce the liver. That evolutionary-developmental interaction is significant because the liver provides regulated sources of glucose and glycogen to the evolving physiologic system, which is necessary for the evolution of the neocortex. Evolution of neocortical control furthers integration of physiologic systems. Such an evolutionary vertical integration of cell-to-tissue-to-organ-to-physiology of intrinsic cell–cell signaling and extrinsic factors is the reverse of the ''top-down'' conventional way in which physiologic systems are usually regarded. This novel mechanistic approach, incorporating a ''middle-out'' cell–cell signaling component, will lead to a readily available algorithm for integrating genes and phenotypes. This symposium surveyed the phylogenetic origins of such vertically integrated mechanisms for the evolution of cell–cell communication as the basis for complex physiologic traits, from sponges to man.

Introduction

Research in physiology and biomedicine is stagnating, particularly when considering all the technologies to which we now have access. A recent Blue Ribbon Panel of the American Academy of Arts and Sciences charged with determining how to ameliorate the crisis in US funding for biomedical research recommended investing in young scientists and in High-Risk, High-Reward Research (The American Academy of Arts and Sciences 2008). This problem is far more fundamental. It is due to the lack of an effective and accessible algorithm for readily translating genes into phenotypes. The problem is quite apparent when compared to the advances in physics over the past 150 years, starting with the Mendeleev version of the periodic table, followed by Quantum Physics and Einstein's formulation of $E=MC^2$. Ironically, Darwin set us off in search of our evolutionary origins (Darwin 1882) at about the same time that Mendeleev formulated his periodic table of elements. That contrast is now underscored by the publication of the Human Genome Project (HGP) in 2000, which sorely lacks an algorithm to convert genes into phenotypes.

To some extent, the failure to advance biomedicine is due to the false hope raised in the wake of the HGP by the promise of Systems Biology (Hood et al. 2008) as a ready means of reconstructing physiology

From the symposium ''Cell–Cell Signaling Drives the Evolution of Complex Traits'' presented at the annual meeting of the Society for Integrative and Comparative Biology, January 3–7, 2009, at Boston, Massachusetts.
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Integrative and Comparative Biology, volume 49, number 2, pp. 142–154
doi:10.1093/icb/icp017
Advanced Access publication May 11, 2009

from genes. Like the atom in Physics, the cell is the smallest functional unit of biology; trying to reassemble Gene Regulatory Networks (GRNs) without accounting for this fundamental feature of evolution will result in a genomic atlas, but not an algorithm for functional genomics. Indeed, the reductionist premise of Systems Biology is reflective of a recurrent pattern in evolutionary biology, vacillating between genes and phenotypes over its stormy history (Gilbert et al. 1996). As a result, the existence of morphogenetic fields has only recently been recognized (Gilbert et al. 1996). The scientific validity of morphogenetic fields has been borne out by contemporary molecular embryology (Walkley et al. 2000; Horowitz and Simons 2008; Rosenblum 2008), beginning with the breakthrough discovery of Homeobox Genes (McGinnis et al. 1984; Scott and Weiner 1984), demonstrating the homologies across phyla first proposed by Geoffroy St-Hillaire in the nineteenth century (Gilbert et al. 1996).

The HGP culminated in the unexpected finding that humans are composed of only 20–25,000 protein coding genes (International Human Genome Sequencing Consortium 2004), whereas a carrot has 40,000, indicating that genes are somehow recombined and permuted in different adaptive ways through mechanisms of evolution. Physiologic systems have evolved through emergent and contingent processes of Natural Selection due to selection pressure for cell-molecularly based adaptation. The foundations of physiology will ultimately be revealed through the effective application of genomic mechanisms to the processes underlying evolutionary-developmental biology. In the current scientific research environment, however, such an integrated process remains fallow, largely because evolutionists are not trained in reductionist research methods, and developmental biologists are not trained in evolutionary methods (Akam 1998).

Following is a mechanistic approach to understanding the principles of physiology based on evolutionary precepts, which challenges the prevailing descriptive paradigm. It was motivated by our recent insights to the cell-molecular mechanisms of lung evolution, which integrates cell–cell signaling mechanisms common to embryogenesis, homeostasis and regeneration (Torday and Rehan 2004).

We would like to use a metaphor to orient the reader toward the ultimate mechanistic perspective taken in this Review. Both physiology and evolution are emergent and contingent, like the weather or the stock market. Evolutionists have dealt with this complex problem by reducing it to phenotypes and genes, yet like the duality of the candlestick/profile

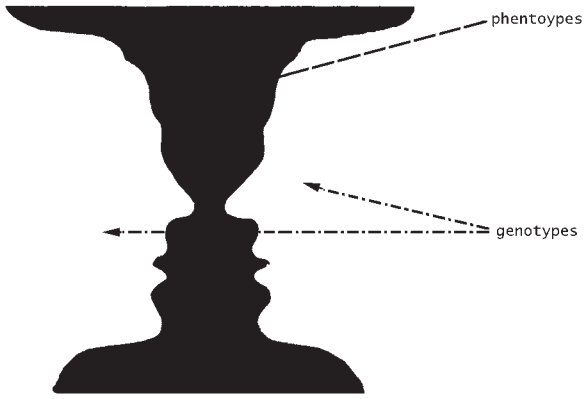

Fig. 1 Figure-ground is a Gestalt psychology principle first introduced by the Danish phenomenologist Edgar Rubin in 1915.

icon used in Gestalt Psychology (Fig. 1), in reality evolution constitutes both, and Natural Selection acts on the phenotype to select for the genetic characteristic(s). The question then is what integrates the mechanisms for this selection process?

Cell–cell signaling and alveolar development: a "reductionist" approach to the evolution of physiologic traits

Primordial lung endoderm and mesoderm interact over the course of lung morphogenesis to differentiate into over 40 different cell types (Sorokin 1960), culminating in the production of pulmonary surfactant. We know a great deal about how growth factor signaling determines these processes and the downstream signals that alter nuclear expression. This ultimately led to metabolic cooperativity between unicellular organisms mediated by ligand–receptor interactions and cell–cell signaling, culminating in homeostasis.

We have learned much about pulmonary biology over the past 50 years by focusing on lung surfactant, the major chemical principal underlying alveolar structure and function. The physiologic significance of lung surfactant was first demonstrated by Avery and Mead (1959), who showed that infants dying of Hyaline Membrane Disease were surfactant deficient. King and Clements (1972) were the first to chemically define the surfactant. Since then the basic cell–molecular biology of the surfactant system has been reduced to a process of communication between the alveolar interstitial lipofibroblast and its neighboring alveolar type II cell, which produces both the surfactant phospholipids and proteins. Similarly, Darwin reduced eye evolution to the interactions between the two cell-types that produce rhodopsin (De Robertis 2008), the chemical principle for vision.

A rather simple solution to the problem of linearity of biosynthetic pathways was described by Horowitz (1945) by assuming a retrograde mode of biochemical pathway evolution, as follows: originally, a given organism could not synthesize a particular biological ''X'', and so it had to acquire it from the surrounding environment. When the supply of X in the environment was exhausted, those organisms which expressed the last enzyme in the X pathway could make use of the immediate precursor and convert it to the end-product, until the supply of the intermediate product was also exhausted. Then only those organisms that possessed the second-to-last enzyme in the X pathway could survive, and so on, iteratively, until the biosynthetic pathway for X was completely established. The power of this perspective for our understanding of the evolution of physiologic processes is that it provides a cell-molecular mechanism for selection pressure that generates complex systems, as will be elucidated.

Even to the naïve observer, it is intuitively obvious that there are patterns of size and shape in biology. Darwin was a master at delineating these patterns and defining a process by which they might have evolved through ''descent with modification,'' as well as a descriptive mechanism—''Natural Selection.'' Such descriptive metaphors are grossly inadequate in the age of genomics because they do not provide the method for reducing evolution to its genetic underpinnings, and therefore they do not generate testable, refutable hypotheses at the gene level. Without an understanding of how and in adaptation to what evolution has occurred, like the Big Bang Theory in physics, we cannot take advantage of the underlying principles, particularly as they might apply to human physiology and medicine. This problem arises repeatedly in various ways that are referred to euphemistically as ''counterintuitive,'' which is an expedient way of dismissing observations that cannot be explained by the prevailing descriptive paradigm. For example, organ systems co-evolved that link lipid metabolism and respiration (alveolar surfactant and gas exchange), photoreception and circadian rhythms (the pineal as the ''third eye''), blood volume control and erythropoiesis, or why ear ossicles evolved from fish jaws—these relationships are seemingly counterintuitive based on descriptive biology. This may be due to the lack of a functionally relevant perspective on the process of evolution.

Alternatively, with the huge challenge of implementing genomics to understand biology, we have reconsidered the process of evolution from a cellular-molecular signaling perspective, because it is where more complex structures and functions evolved from (King et al. 2003; De Robertis 2008). Such a Kuhnian paradigm shift, demanding a change in the language of evolutionary biology, would allow us to distinguish ''forest and trees,'' and how an understanding of the evolution of structure and function lends itself to the application of genomics to medicine. It seems intuitively obvious that there are fundamental commonalities between ontogeny and phylogeny, given that both start from single cells, and form progressively more complex structures through cell–cell interactions mediated by growth factors and their receptors. By systematically focusing on such cell-molecular developmental mechanisms as serial events across vertebrate classes, we can test the inferences of cladograms using falsifiable hypotheses based on descent with modification.

An integrated, empiric, middle-out approach to physiology

The greatest challenge in the postgenomic era is to effectively integrate functionally relevant genomic data in order to derive physiologic first principles, and determine how to use them to decode complex traits. Currently, this problem is being addressed stochastically by analyzing large data sets to identify genes that are associated with structural and functional phenotypes—whether they are causal is indeterminate. This approach is merely an extrapolation from systematic biology since Linnaeus. The reductionist genetic approach cannot simply be computed to generate phenotypes (Polanyi 1968; Macklem 2008)—evolution is not a result of chance; it is an ''emergent and contingent'' process. In our current and future research environment we must expand our computational models to encompass a broad, evolutionary approach—as Dobzhansky (1973) has famously said, ''Nothing in biology makes sense except in the light of evolution.'' We have formally proposed using a comparative, functional genomic middle-out approach to solve for the evolution of physiologic traits. The approach engenders development, homeostasis and regeneration as a cluster of parallel lines that can be mathematically analyzed as a family of simultaneous equations (Torday and Rehan 2004). This perspective provides a feasible and refutable way of systematically integrating such information in its most robust form to retrace its evolutionary origins (Fig. 2). Among mammals, embryonic lung development is subdivided into two major phases: branching morphogenesis and alveolization. Fortuitously, we have observed that deleting the parathyroid hormone-related protein (PTHrP) gene results in failed alveolization

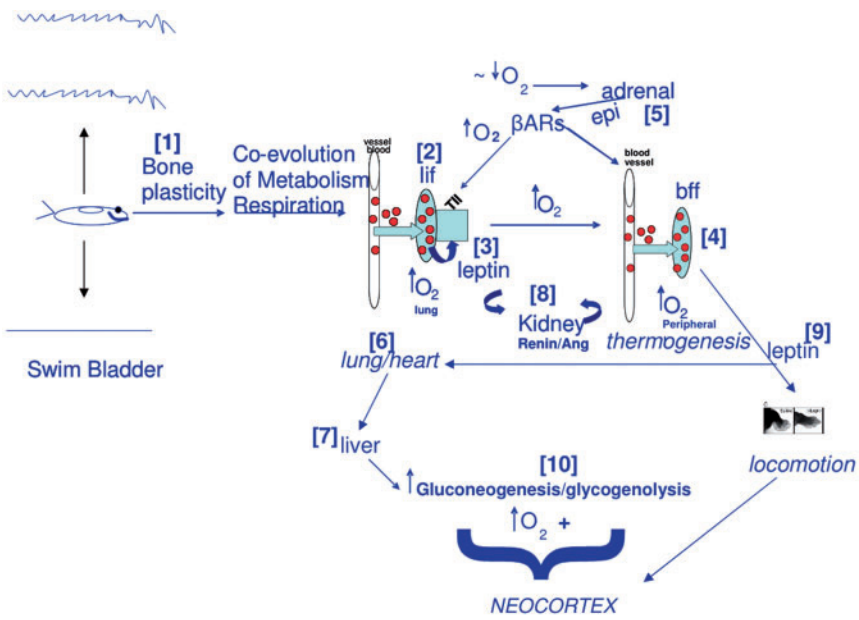

Fig. 2 Emergent and contingent evolution from cells to systems. The swim bladder, an out-pouching of the gut in physostomus fish, produces surfactant, facilitating its expansion and contraction ("stretch"), allowing controlled buoyancy for feeding efficiency in adaptation to gravity. [1] The swim bladder gave rise to the functionally homologous lung surfactant system. [2] Environmental oxygen induced the differentiation of muscle stem cells into lipofibroblasts (lif) in the lung [2], promoting oxygen uptake by leptin stimulation of surfactant production [3], resulting in increased circulating oxygen, inducing peripheral fat cells [4]. Functional hypoxia due to evolving metabolic demand for oxygen created selection pressure for adrenal beta-adrenergic signaling [5] resulting in independent blood pressure regulation of the lung and systemic circulation. Co-evolution of lung and heart structure-function [6] resulting in increased heart size, caused precocious liver development for glucose homeostasis [7]. Co-evolution of the kidney renin/angiotens in system [8] provided further integrated blood pressure regulation. Leptin production by fat cells [9] evolved metabolic integration of limb and lung development. The resultant integrated regulation of oxygen and glucose [1–9] promoted neocortical evolution [10].

(Rubin et al. 1994). The generation of progressively smaller, more plentiful alveoli with thinning walls because gas exchange was necessary for the transition from water to air. This, and the fact that PTHrP and its receptor are highly conserved [the PTHrP ortholog Tuberoinfundibular Protein (TIP39) is expressed as far back in phylogeny as yeast], is stretch-regulated, and forms a paracrine signaling pathway mechanistically linking the endodermal and mesodermal germ layers of the embryo to the blood vessels, has compelled us to exploit this key transitional GRN to further our understanding of physiology based on first principles. This model can transcend the lung based on ontogenetic and phylogenetic principles: PTHrP produced by the lung epithelium regulates mesodermal leptin through a receptor-mediated mechanism. We have implicated leptin in the normal paracrine development of the lung, demonstrating its effect on lung development in the *Xenopus* tadpole (Torday et al. 2009), for the first time providing a functional, cell-molecular mechanism for the often described co-evolution of metabolism, locomotion and respiration (Duncker 2004; Hillenius and Ruben 2004). These experiments have led to the question as to why the lipofibroblast appears in vertebrate lung alveoli, starting with reptiles: the introduction of the lipofibroblast, an adipocyte-like mesenchymal derivative of the splanchnic mesoderm, could have evolved as an organizing principle for PTHrP/PTHrP receptor-mediated alveolar homeostasis, as follows. Leptin is a ubiquitous product of adipocytes, which binds to its receptor in the alveolar epithelium of the lung, stimulating surfactant synthesis (Torday and Rehan 2002; Torday et al. 2002), reducing surface tension, generating a progressively more compliant structure on which selection pressure could ultimately select for the stretch-regulated PTHrP co-regulation of surfactant and microvascular perfusion. This mechanism could have given rise to the mammalian lung, with maximal surface area resulting from stretch-regulated surfactant production and alveolar capillary perfusion (Gao and Raj 2005), thinner alveolar walls due to PTHrP's apoptotic effect on fibroblasts (Chen et al. 2002), and a reinforced blood–gas barrier due to the evolution of type IV collagen (West and Mathieu-Costello 1999). This last feature may contribute generally to the molecular bauplan

for the peripheral microvasculature of evolving vertebrates.

The Berner hypothesis and the emergence of adipocytes: on the evolutionary origins of the lipofibroblast

Given the central role of the lipofibroblast in vertebrate lung evolution, both as a cytoprotective mechanism against oxygen free radicals (Torday et al. 2001), and as an integrator of stretch-regulated surfactant production (Torday 2003), one might ask how and why it evolved. Csete et al. (2001) observed that cultured muscle stem cells spontaneously differentiate into fat cells in 21% oxygen, but not in 6% oxygen. This experimental observation is provocative in the context of the episodic rises and falls in atmospheric oxygen over the past 500 million years, as shown by Berner et al. (2007), suggesting that the increases in atmospheric oxygen may have induced adipocytes over the course of vertebrate evolution. Our laboratory has shown that the muscle-derived adipocytes in the lung protect it against oxidant injury (Torday et al. 2003), and promote surfactant synthesis by producing leptin (Torday and Rehan 2002; Torday et al. 2002). Both of these features would have facilitated the vertebrate transition from water to land, and may have fueled the progressive increase in oxygenation from amphibians to mammals by increasing alveolar distensibility (Torday 2003). Also, the hyperoxic stimulus for lung evolution may have been synergized by the accompanying decreases in atmospheric oxygen, since hypoxia is the most potent physiologic stimulant for adrenaline production. Thus, the episodic fluctuations in atmospheric oxygen would have reinforced the selection pressure on the βAR mechanisms for alveolar homeostasis, including surfactant production, fluid balance and microcirculatory blood pressure regulation.

A natural consequence of the increase in tissue oxygenation resulting from the evolution of the lung is the differentiation of peripheral muscle stem cells into fat cells (Csete et al. 2001) and the evolution of endothermy (Mezentseva et al. 2008). Endothermy requires increased metabolic activity, putting further selection pressure on the cardiopulmonary system. Since the increase in body temperature from cold (25°C) to warm-blooded organisms (37°C) alone would have increased surfactant phospholipid activity 300% (Daniels and Orgeig 2003). For example, Map turtles show different surfactant compositions depending on their environmental temperature (Lau and Keough 1981). Therefore the advent of thermogenesis would have been facilitated by the physical increase in lung surfactant activity. These synergistic selection pressures would have been further enhanced directly by the coordinate effects of beta-adrenergic agents on the heart (Brodde 1990), lung (Warren 1986) and fat depots (Lafontan et al. 1997), and indirectly by the increased production of leptin by fat cells, which is known to stimulate vasculogenesis (Wolk et al. 2005) and osteogenesis (Hamrick 2004), accommodating the infrastructural changes necessitated by the evolution of complex physiologic traits. Crespi and Denver (2006) have shown that leptin stimulates both food intake and limb development in *Xenopus laevis* tadpoles, linking metabolism and locomotion through this pleiotropic mechanism. Importantly, we have subsequently reported that leptin also stimulates lung development in *X. laevis* tadpoles (Torday et al. 2009), linking metabolism, locomotion and respiration—the three major elements of animal evolution—together mechanistically for the first time through these pleiotropic effects of leptin.

Based on this cell-molecular functional genomic connection between molecular oxygen, adipogenesis, leptin and the evolution of land vertebrates is like Theseus following the string to get out of the Labyrinth! Evolutionary biology needs more of such experimental models based on refutable hypotheses to solve the evolutionary puzzle—i.e., the systematic identification of evolved physiologic traits, which, when reduced to those cell-molecular features that have been modified by descent, can be experimentally tested. For example, we are expanding our experiments on the effects of leptin on lung development in Xenopus (Torday et al. 2009) to determine how it affects the blood–gas barrier basement membrane and vasculature. In the future we will determine if the same cell-molecular mechanisms apply to fish, reptiles, birds, and mammals, or not. The message is that the elucidation of the mechanistic origins of homologies is an experimentally soluble problem.

Lung biology as a Cipher for evolution

The lung is an on "demand system," i.e., the production of surfactant, alveolar capillary blood flow and type IV collagen synthesis are all under the control of the PTHrP-leptin stretch mechanism. Why? In theory these processes could have functioned at full capacity due to Neutral Theory (Kimura 1983) or Natural Selection, as suggested by the Symmorphosis hypothesis (Weibel et al. 1998). Instead, the

mechanisms are now, and were, functionally adapted to the prevailing conditions, which might be seen as being "costly" based on conventional *ex post facto* physiologic analyses. When seen from an evolutionary perspective, as an epistatic mechanism, adaptations, in the aggregate, ultimately represented an "all or nothing," "life or death" survival of the fittest event. Indeed, when looked at from that vantage point, the evolution of the lung from the swim bladder now provides a rational explanation for the "on demand" mechanisms of lung physiology because the expansion and contraction of the swim bladder with air as an adaptation to gravity was the basic bauplan. It provided the physiologic basis for the emergence of the alveolus as the organ of gas exchange. As a note in support of this concept, when Weibel et al. (1998) tested the symmorphosis principle in the lung, they concluded that it was "over-engineered," i.e., had far more capacity than was required by physiologic criteria. That may be because the lung initially evolved for buoyancy.

Functional relationship between the external and internal "environments"

The foregut is a plastic structure from which the thyroid, lung and pituitary arise through TTF-1/Nkx2.1 expression (Bingle 1997; Ao et al. 2004). Evolutionarily, this is consistent with the concept of "terminal addition" since the deuterostome gut is formed from the anus to the mouth. When Nkx 2.1/TTF-1 is knocked out in embryonic mice, the thyroid, lung and pituitary do not form during development (Takuma et al. 1998; Yuan et al. 2000; Kusakabe et al. 2006), providing experimental evidence for the genetic commonality of all three organs. Their phylogenetic relationship has been traced back to amphioxus, and to cyclostomes, since the larval endostyle, the structural homolog of the thyroid gland (Kluge et al. 2005), expresses Nkx 2.1/TTF-1 (Ogasawara et al. 2001).

Mechanistically, the increased bacterial load due to the facilitation of feeding by the endostyle may have stimulated the cyclic A-dependent protein kinase A pathway since bacteria produce endotoxin, a potent PKA agonist. (This cascade may have evolved into regulation by Thyroid Stimulating Hormone of the thyroid since it acts on the thyroid via the cAMP-dependent PKA signaling.) This mechanism potentially generated novel structures like the thyroid, lung, and pituitary, all of which are induced by the PKA-sensitive TTF-1/Nkx2.1 pathway. Developmentally, the thyroid evaginates from the foregut in the mouse beginning on day 8.5, one day before the lung and pituitary emerge, suggesting that the thyroid may have been a molecular prototype of the lung during evolution, providing a testable, and refutable hypothesis. The thyroid rendered molecular iodine in the environment bioavailable by binding it to threonine to generate thyroid hormone, whereas the lung made molecular oxygen bioavailable, first by inducing fat cell-like lipofibroblasts as cytoprotectants (Torday et al. 2001), which then stimulated surfactant production by producing leptin (see above), placing increased selection pressure on the blood–gas barrier by making the alveoli more compliant. This in turn may have created further selection pressure for the metabolic system to utilize the rising oxygen in the environment, placing further selection pressure on the alveoli, giving rise to the stretch-regulated surfactant system mediated by PTHrP, and leptin (Torday and Rehan 2002; Torday et al. 2002). Subsequent selection pressure on the cardiopulmonary system may have facilitated liver evolution, since the progressively increasing size of the heart may have induced precocious liver development (Rossi et al. 2001), fostering increased glucose regulation. The brain is a glucose "sink," and there is experimental evidence that increasing glucose during pregnancy increases the size of the developing brain (Saintonge and Cote 1984). The further evolution of the brain would have served to further the evolution of complex physiologic systems.

Both the thyroid and lung have played similar adaptive roles during vertebrate evolution. The thyroid has facilitated the utility of iodine ingested from the environment, whereas the lung has accommodated the rising oxygen levels during the Phanerozoic era. In both cases, these structures have accommodated otherwise toxic substances for biologic purposes that have allowed vertebrates to adapt to their environment. Importantly, the thyroid and lung may have interacted cooperatively in facilitating vertebrate evolution. Thyroid hormone stimulates embryonic lung morphogenesis during development (Sullivan et al. 2003), while also accommodating the increased lipid metabolism needed for surfactant production (see above) by driving fatty acids into muscle to increase motility, as opposed to circulating lipids being oxidized to toxic lipoperoxides. The selection pressure for metabolism was clearly facilitated by the synergy between these foregut derivatives.

From fat cells to integrated physiology

We have previously addressed the developmental, homeostatic, regenerative, and evolutionary roles of

the lipofibroblast (Torday and Rehan 2004, 2007a, b) by identifying key GRNs relevant to the evolution of the lung—namely the PTHrP/leptin GRN that determines the development, homeostasis, and regeneration of the alveolus. By focusing on this key paracrine mechanism, we have been able to identify genes expressed in lipofibroblasts up-stream from the surfactant mechanism that are highly conserved in vertebrate physiology, namely PPAR gamma (Hu et al. 1995), ADRP (Schultz et al. 2002), and leptin (Torday et al. 2002). The stretch regulation of lung surfactant by PTHrP likely refers back to the swim bladder origins of the lung, since the swim bladder integrates the physical adaptation to gravity, i.e., buoyancy, with feeding efficiency. The relevance of PTHrP to lung evolution was first suggested by the lung phenotype in the PTHrP knockout mouse, since the absence of PTHrP resulted in failed alveolar formation, suggesting its principal role in lung evolution. The evolution of the lung is characterized by the progressive phylogenetic decrease in alveolar diameter, increasing the gas exchange surface area for gas exchange from fish to man (Daniels and Orgeig 2003). That progression would not have been physically possible without the accompanying increase in the efficiency of surfactant synthesis to reduce alveolar surface tension, since the law of Laplace determines that the smaller the surface area of a sphere, the higher the surface tension.

In retrospect, experimental evidence for the evolutionary interrelationship between surfactant and stretching was first provided by Clements et al. (1970), when they demonstrated a linear interrelationship between alveolar surface area and the amount of surfactant per unit area across a wide range of vertebrate species, ranging from frogs to cows. In the interim, there have been numerous experiments demonstrating the on-demand production of surfactant in response to increased tidal volume, i.e., alveolar distension (Wyszogrodski et al. 1975; Nicholas et al. 1982), culminating in a series of studies from our laboratory showing how the stretching of the alveolus determines its physiological adaptation, and plasticity via the PTHrP/leptin signaling pathway (Torday and Rehan 2007a, b).

The evolutionary significance of this mechanism is further underscored by the pleiotropic effects of PTHrP and leptin on other physiologically integrated principles of the alveolus: the potent vasodilatory effect of PTHrP (Gao and Raj 2005) facilitated alveolar ventilation–perfusion matching, the physiologic integration of alveolar expansion and contraction with alveolar capillary perfusion, further enhancing the efficiency of gas exchange by coordinating lung tidal volume with both surface activity and alveolar capillary blood flow (V/Q matching). Also, the evolved regulation of type IV collagen is indicative of the physiologic monitoring of the blood–gas barrier, as first suggested West and Mathieu-Costello (1999).

Ontogeny of the beta-adrenergic receptor and the evolution of physiologic systems

The evolution of the alveolar bed as an efficient means of gas exchange generated progressively greater selective pressure for thinning the membranes through which gas exchange takes place, specifically for the independent regulation of the pulmonary and systemic blood pressures (West and Mathieu-Costello 1999). Without a means of independently regulating the two circulatory systems, the lung alveolar microvasculature would have limited the efficiency of gas exchange. This was accommodated by the evolution of the beta-adrenergic receptor (βAR) mechanism, consisting of receptors in the lung for adrenaline produced by the adrenal medulla (Mutlu and Factor 2008). Adrenaline is critically important for both alveolar homeostasis (Mutlu and Sznajder 2005) and for the transition from intrauterine to postnatal life (Folkesson et al. 2002), since adrenaline facilitates the removal of lung liquid from the alveoli at the time of birth, and concomitantly stimulates alveolar secretion of surfactant. The ontogenetic appearance of βARs in the lung alveolar epithelium at the time of birth integrates whole animal physiology and the reproductive process (Phillippe 1983). In the absence of adequate βAR activity, the newly born infant would literally "drown" in its own pulmonary secretions.

In fish, the adrenal medulla and cortex are separate structures. The selection pressure for adrenal regulation of pulmonary blood pressure may have been the selective force behind the further evolution of the adrenal cortex becoming integral to the medulla. Functionally, glucocorticoids produced in the adrenal cortex drain through the adrenomedullary arcades, stimulating Catechol-*O*-methyl transferase synthesis (Parvez and Parvez 1973), the rate-limiting step in adrenaline synthesis, on the one hand, and stimulating the number of βARs, which enhances adrenaline action on the lung under stress conditions, on the other. This close physiologic functional integration of the adrenocorticomedullary and pulmonary systems during the birth process may have generated the selection for hormonal acceleration of the lung's development

(Ballard and Ballard 1996), providing phenotypic variability in the rates of pulmonary development that enhanced survival under such conditions as famine (O'Regan et al. 2001), infection (Rehan et al. 2007) and physiologic stress (Amiel-Tison et al. 2004). The causal nature of this evolved mechanism is further supported by the antagonistic effect of adrenocortical androgens on this process (Torday 1990), indicating co-evolution of both agonistic, and antagonistic effects of the endocrine system on the lung that have generated a spectrum of phenotypes, or a reaction norm, that optimizes both physiological and structural adaptation.

Molecular homologies distinguish evolutionary "forest and trees"

The central premise of this article is that there are molecular homologies that underpin seemingly disparate physiologic phenotypes. Those homologies can be visualized through the "prism" of developmental and phylogenetic cell-molecular mechanisms (Holland and Holland 1999). For example, we have been able to reduce metabolic adaptation of terrestrial vertebrates to the induction of adipocytes by oxygen, both in the lung and in the periphery. Moreover, the fat–cell product leptin has pleiotropic effects on the development of the lung (Torday 2002; Torday and Rehan 2002), vasculature (Wolk et al. 2005), bone (Hamrick 2004), and central nervous system (O'Malley et al. 2007), providing a mechanistic link between adipocytes and the evolution of complex physiologic structures and functions. Empiric evidence for these mechanistic interrelationships comes from the mouse knockout for PPAR gamma, the nuclear transcription factor that determines the adipocyte phenotype that generates both fat (Medina-Gomez et al. 2007) and lung (Simon et al. 2006) phenotypes. As further evidence for the role of leptin in normal lung development, the leptin deficient Ob/Ob rat lung is hypoplastic (Huang et al. 2008).

Our ability to test the hypothetical linkage between adipocyte production of leptin and the evolution of complex physiologic traits has more recently been facilitated by the discovery that specific micro RNAs, which are endogenously expressed 20–24 nucleotide RNAs thought to repress protein translation through binding to a target mRNA (Esau et al. 2004), are determinants of the adipocyte phenotype. Only a few of the more than 250 predicted human miRNAs have been assigned any biological function. The miR-143 levels increase during adipocyte differentiation, and inhibition of miR-143 effectively inhibits adipocyte differentiation. In addition, protein levels of the proposed miR-143 target ERK5 are affected by miR-143 antisense oligonucleotide-treated adipocytes, demonstrating the causal relationship between miR-143, ERK5 and adipocyte differentiation. MiR-103 and -107 have also been shown to play roles in adipogenesis (Wilfred et al. 2007).

Vertical integration provides the basis for the translation of genomics into the periodic table for biology

Our evolutionary-developmental paradigm for lung biology can be expanded to a systems biology-like approach through a number of avenues (Fig. 2). Embryologically, as we have already indicated, the PTHrP signaling pathway is up-stream from the endocrine mechanisms that determine development of the lung, incorporating the endocrine system into the model. Furthermore, the lung is embryologically derived from the gut, which develops through similar gene regulatory pathways, thus integrating the gut and its derivatives—liver, pancreas, thyroid, and pituitary—into the model. These developmental interrelationships can be further exploited by characterizing the GRNs that determine them. For example, we have demonstrated the centrality of both the Wnt/beta catenin and G-protein coupled protein kinase A pathways in the epithelial–mesenchymal interactions that determine pulmonary structure and function. These same epithelial–mesenchymal interactions determine the structure and function of a broad variety of tissues and organs (kidney, liver, pancreas, gut, thyroid, adrenal, thymus, eye, and skin). And the central role of PPAR gamma as the determinant of the lung fibroblast GRNs mechanistically engenders such seemingly disparate tissues and organs as the brain, bone marrow, liver, and adipose tissue, all of which are also phenotypically PPAR gamma-dependent.

The networks of genes that derive from the proposed algorithm generated using a self-organizing map approach such as the one previously proposed (Torday 2004) would link specific phenotypes together in ways that seem counterintuitive, offering dynamic new ways of thinking about how the genomic "elements" of physiologic systems are recombined and permuted through evolution to generate novelty based on cellular principles of phylogeny and development, rather than on static descriptions of structure and function. This is analagous to the periodic table being based on atomic number as an independent "organizing

mechanism'' for the physical elements. And like the periodic table of elements, which predicted other elements, the biologic algorithm will predict novel GRNs. Ultimately, this biologic space–time hologram will reveal the underlying rules for the first principles of physiology. Our laboratory has devised several models with which to test this evolutionary cell-molecular concept, the developing rat and mouse, the embryonic chick, and the *Xenopus* tadpole. These models offer a concerted developmental and phylogenetic approach for determining specific functional GRNs across phyla.

This is not a "Just So Story"

Unlike Kipling's Just So Stories about how and why the leopard got its spots, the rhinoceros got its tough skin, or the camel got its hump, the cell–cell signaling model of physiologic evolution is not a 'just so story.' It is based on evolved mechanisms of cell-molecular embryogenesis, culminating in homeostasis. When such evolved structure–function relationships fail, they recapitulate the developmental/evolutionary mechanisms (Bacallao and Fine 1989; Torday and Rehan 2007a, b; Königshoff et al. 2008). Unlike the classic pathophysiologic approach to disease, which reasons backwards from disease to health, the evolutionary-developmental approach, like Fig. 2, reasons from the cellular origins of physiology, resulting in prediction of the cause of chronic disease, as we have shown for the lung (Rehan and Torday 2006) and Fine has shown for the kidney (Bacallao and Fine 1989). As proof of principle, we will cite three examples of the fundamental difference between a pathophysiologic and an evolutionary approach to disease. Based on our own work, we have been able to effectively prevent the chronic lung disease of the newborn, Bronchopulmonary Dysplasia (BPD), experimentally, based on principles of pulmonary cell-molecular evolution (Torday and Rehan 2007a, b). Unlike conventional chronic lung diseases, which are seen as the result of inflammation, BPD is caused by prematurity independent of inflammation—just overdistending the preterm lung or exposing it to room air can cause BPD.

As further evidence for the predictive power of the physiologic evolutionary approach, it provides a mechanistic link between the lung and kidney in Goodpasture's Syndrome (MacDonald et al. 2006). This abnormality is instructive in showing how the evolutionary approach to health and disease can uncover relationships that have remained enigmatic by the conventional pathophysiologic approach for decades. The same type IV collagen autoimmune abnormality exists for both the lung and kidney, due to the formation of autoantibodies against the three alpha isoform, providing a pathological connection between adaptive barrier function in the alveolus and glomerulus in this epithelial basement membrane disease. In their elucidation of the evolution of the Goodpasture's Syndrome antigen, MacDonald et al. (2006) showed that the alpha three chain of type IV collagen did not cross-react with the Goodpasture antibody in worms, flies or fish, but did in frogs, chickens, mice, and humans. Three-dimensional molecular modeling of the human type IV collagen 3 alpha revealed an evolutionary alteration of electrostatic charge and polarity due to the emergence of critical serine, aspartic acid, and lysine residues, along with loss of asparagine and glutamine, resulting in the emergence of the two major Goodpasture epitopes. Goodpasture's Syndrome is rare, occurring in only one in 100,000 people, suggesting that the increased hydrophobicity and electrostatic charge of the molecule may have conferred a biologic selection advantage. Both the alveolus and glomerulus are physiologic barriers which must keep the serum and proteins in the capillaries out of the extracellular space. The increased hydrophobicity of the evolved form of type IV collagen 3 alpha would inhibit fluid exudation, preventing alveolar capillary leak, and the increased negative charge would repel the mostly negatively charged proteins in circulation. Both the alveolus and glomerulus monitor pressure changes—air in the case of the former, fluid in the case of the latter—which are highly evolved physiologic mechanisms. These overall commonalities are underpinned by common cell-molecular mechanisms of adaptation. In both the alveolus and glomerulus, PTHrP signaling by homeostatic fibroblasts is the cell-molecular evolutionary link—in the alveolus, PTHrP is necessary for lipofibroblast signaling and surfactant regulation (Torday et al. 2002); in the glomerulus, podocyte PTHrP production is essential for the mesangial cell phenotype and functional regulation of fluid volume (Bosch et al. 1999a, b). As further proof of principle, in both cases the biologic reactions to the failure of these evolved phenotypes are virtually the same—failure of PTHrP signaling in both the alveolus and glomerulus results in the formation of myofibroblasts due to the breakdown in PTHrP-mediated cell–cell signaling (Bosch et al. 1999b; Torday et al. 2002). These interrelationships may ultimately provide an explanation for Potter's Syndrome, in which decreased renal function idiopathically leads to oligohydramnios

and consequent pulmonary hypoplasia due to lack of fluid distension.

Similarly, the etiology of osteoporosis may be better understood using the evolutionary-functional genomic approach. Based on conventional pathophysiology, the bone-wasting disease osteoporosis, which occurs in post-menopausal women, has been attributed to decreased estrogen production (Utian et al. 2008). This same disease occurs in male Astronauts, who, by definition, do not suffer from decreased estrogen production, yet this same endocrine mechanism is being applied. On the contrary, we have implicated microgravitational effects of PTHrP in this process based on an evolutionary adaptational mechanism whereby the tension of muscle on bone causes locally increased PTHrP production, maintaining calcium homeostasis (Torday 2003). This evolutionary interrelationship between mechanotransduction and bone calcification is consistent with studies of calcification in atherosclerosis. Here, too, signaling for calcium homeostasis may come into play when the normal homeostatic mechanisms fail, perhaps as a (mal)adaptive means of maintaining vascular blood flow.

As an example of how an evolutionary approach can facilitate understanding complex neurologic diseases, in a recent study conducted at the University of Utah, investigators hypothesized that the high-intelligence test scores among Ashkenazi Jews are a consequence of their occupation of a social niche over the last millennium that selected strongly for intelligence (Cochran et al. 2006). The investigators went on to suggest that there was an increase in the frequency of specific genes that caused this increased intelligence, which also led to an increased incidence of hereditary neurologic disorders characterized by abnormal neuronal myelinization. The mechanisms that favored increased neuralization pathways for intelligence inadvertently gave rise to such neurodegenerative diseases as Tay-Sachs, Gaucher's, Niemann-Pick, and mucolipidosis type IV, all of which are lysosomal storage diseases. The increase in storage of glucosylceramide in Gaucher's, for example, promotes axonal growth and branching (Schwarz et al. 1995). Similarly, in Tay-Sachs and Niemann-Pick, increased GM2 ganglioside causes increased dendritogenesis (Walkley et al. 2000; Walkley 2003).

Three thousand years of descriptive biology and medicine have brought us to the threshold of molecular medicine. Now, aided by our knowledge of the Human Genome, we must address the evolutionary origins of human physiology based on phylogenetic and developmental mechanisms. The approach we have proposed may fail to directly identify such first principles because we are missing intermediates from the "molecular fossil record" that failed to optimize survival. But some vestiges of those "failures" were likely incorporated into other existing functional phenotypes, or into other molecularly related functional homologies, like those of the lung and kidney, photoreceptors and circadian rhythms, the lens and liver enzymes. What this approach does provide is a robust means of formulating refutable hypotheses to determine the ultimate origins and first principles of physiology by providing candidate genes for phenotypes hypothesized to have mediated evolutionary changes in structure and/or function. It also forms the basis for predictive medicine (Torday and Rehan 2009) rather than merely showing associations between genes and pathology, which is an unequivocal Just So Story. In this new age of genomics, our reach must exceed our grasp.

Funding

National Institutes of Health R01Grants (HL055268 to J.S.T., in part); HD051857 (in part); HL075405 (to V.K.R., in part).

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